

IN THE CLAIMS:

Please cancel claims 1-9, 16, 23, 24, 33, 39-45, and 60, and amend claims 10, 13-15, 17, 20-22, 25-32, 34-38, 46-49, 51-55, 57-59, as follows:

1-9. (CANCELED)

10. (CURRENTLY AMENDED) A method of selecting a molecule of interest that binds to a target ligand, wherein the method comprises:

(1) providing a signal amplification system that comprises a bacterial multi-hybrid system of at least two chimeric polypeptides comprising:

(A) a first chimeric polypeptide comprising a first fragment of an enzyme chosen from adenylate cyclase or guanylate cyclase;

(B) a second chimeric polypeptide comprising a second fragment of an enzyme chosen from adenylate cyclase or guanylate cyclase or a modulating substance capable of activating that activates the enzyme adenylate cyclase or guanylate cyclase;

wherein the first fragment is fused to a molecule of interest and the second fragment or modulating substance is fused to a target ligand;

(2) contacting the molecule of interest and the target ligand;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1); and,

(4) triggering transcriptional activation;

wherein activity of the enzyme is restored by in vivo ~~interaction~~ binding between the molecule of interest and the target ligand, which generates the amplified signal in (3).

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11. (PREVIOUSLY PRESENTED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification comprises the production of a signaling molecule.

12. (PREVIOUSLY PRESENTED) The method of selecting a molecule of interest as claimed in claim 10, wherein the transcriptional activation results in expression of a reporter gene.

13. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme chosen from adenylate cyclase or guanylate cyclase, whose enzymatic activity is restored by ~~the interaction~~ binding between the said molecule of interest and the said target ligand.

14. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme chosen from adenylate cyclase or guanylate cyclase and a modulating substance.

15. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the target ligand is selected from the group consisting of protein, peptide, polypeptide, receptor, antigen, antibody, DNA binding protein, glycoprotein, lipoprotein, ~~[[and]]~~ or recombinant protein.

16. (CANCELED)

17. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein ~~the interaction~~ binding between the molecule of interest and the target ligand is detected by signal amplification that triggers

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transcriptional activation, and is quantified by measuring [[the]] synthesis of a signaling molecule or expression of a reporter gene.

18. (PREVIOUSLY PRESENTED) The method of selecting a molecule of interest as claimed in claim 11, wherein the signaling molecule is a component of a cAMP signaling cascade reaction.

19. (PREVIOUSLY PRESENTED) The method of selecting a molecule of interest as claimed in claim 11, wherein the signaling molecule is a component of a cGMP signaling cascade reaction.

20. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 12, wherein the reporter gene encodes a protein with ~~is a gene with~~ a selectable phenotype.

21. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein an amino acid sequence of the molecule of interest is mutated compared to an amino acid sequence of the wild type molecule and said molecule of interest is tested for its ability to interact-bind with the target ligand.

22. (CURRENTLY AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the selection is performed in a ~~bacterial strain~~ bacteria.

23-24. (CANCELED)

25. (CURRENTLY AMENDED) A method of screening for a substance that stimulates or inhibits the ~~interaction~~ binding between a target ligand and a molecule of interest wherein the method comprises:

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(1) providing a signal amplification system that comprises a bacterial multi-hybrid system of at least two chimeric polypeptides containing:

(A) a first chimeric polypeptide comprising a first fragment of an enzyme chosen from adenylate cyclase or guanylate cyclase;

(B) a second chimeric polypeptide comprising a second fragment of the enzyme chosen from adenylate cyclase or guanylate cyclase or a modulating substance ~~capable of activating said enzyme~~ that activates adenylate cyclase or guanylate cyclase;

wherein the first fragment is fused to a molecule of interest and the second fragment or the modulating substance is fused to a target ligand;

(2) contacting the molecule of interest and the target ligand in the presence of the substance;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1);

(4) triggering or abolishing transcriptional activation,
wherein the activity of the enzyme is restored by *in vivo* interaction between the molecule of interest and the target ligand, which generates the amplified signal in (3);
and

(5) comparing said signal amplification with the one obtained from an identical signal amplification system in the absence of the substance, wherein a difference in the signal amplification in the presence and absence of the substance indicates that the substance stimulates or inhibits ~~the interaction~~ binding between the target ligand and the molecule of interest.

26. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme chosen from adenylate cyclase or guanylate cyclase, wherein the enzymatic activity is restored by the interaction between the molecule of interest and the target ligand.

27. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme chosen from adenylate cyclase or guanylate cyclase and a modulating substance.

28. (CURRENTLY AMENDED) The method of screening for a substance that stimulates ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification comprises the production of a signaling molecule.

29. (CURRENTLY AMENDED) The method of screening for a substance that inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification is blocked or partially abolished.

30. (CURRENTLY AMENDED) The method of screening for a substance that stimulates ~~the interaction~~ binding between a target ligand and a

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molecule of interest as claimed in claim 25, wherein the transcriptional activation results in reporter gene expression.

31. (CURRENTLY AMENDED) The method of screening for a substance that inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the transcriptional activation results in a reporter gene expression which is blocked or partially abolished.

32. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the target ligand is selected from the group consisting of receptor, antigen, antibody, DNA binding protein, glycoprotein, and or lipoprotein.

33. (CANCELED)

34. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule is a component of a cAMP signaling cascade reaction.

35. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule is a component of a cGMP signaling cascade reaction.

36. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and

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a molecule of interest as claimed in claim 30, wherein the reporter gene encodes a protein with ~~is a gene with~~ a selectable phenotype.

37. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the amino acid sequence of the molecule of interest is mutated compared to the amino acid sequence of the wild type molecule and said molecule of interest is tested for its ability to interact with the target ligand.

38. (CURRENTLY AMENDED) The method of screening for a substance that stimulates or inhibits ~~the interaction~~ binding between a target ligand and a molecule of interest as claimed in claim 25, wherein the screening is performed in a ~~bacterial strain~~ bacteria.

39-45. (CANCELED)

46. (CURRENTLY AMENDED) The method as claimed in claim 20, wherein the reporter gene is selected from a gene for synthesis of a nutritional marker, a gene conferring resistance to an antibiotic, a gene encoding a toxin, a gene encoding a color marker, a gene encoding a phage receptor protein, ~~[[and]]~~ or a gene encoding a ~~fragment of a receptor of a phage receptor protein~~ or a fragment thereof.

47. (CURRENTLY AMENDED) The method as claimed in claim 46, wherein the reporter gene encodes a nutritional marker and the nutritional marker is lactose or maltose.

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48. (CURRENTLY AMENDED) The method as claimed in claim 46, wherein the reporter gene encodes resistance to an antibiotic and the antibiotic is ampicillin, kanamycin, or tetracyclin.

49. (CURRENTLY AMENDED) The method as claimed in claim 46, wherein the reporter gene encodes a color marker and the color marker is a fluorescent marker.

50. (PREVIOUSLY PRESENTED) The method as claimed in claim 49, wherein the fluorescent marker is Green Fluorescent Protein.

51. (CURRENTLY AMENDED) The method as claimed in claim 46, wherein the reporter gene encodes a phage receptor protein or a fragment thereof and the phage is phage λ or *lamB*.

52. (CURRENTLY AMENDED) The method as claimed in claim 36, wherein the reporter gene is selected from a gene for synthesis of a nutritional marker, a gene conferring resistance to an antibiotic, a gene encoding a toxin, a gene encoding a color marker, a gene encoding a phage receptor protein, [[and]] or a gene encoding a fragment of a receptor of a phage receptor protein or a fragment thereof.

53. (CURRENTLY AMENDED) The method as claimed in claim 52, wherein the reporter gene encodes a nutritional marker and the nutritional marker is lactose or maltose.

54. (CURRENTLY AMENDED) The method as claimed in claim 52, wherein the reporter gene encodes resistance to an antibiotic and the antibiotic is ampicillin, kanamycin, or tetracyclin.

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55. (CURRENTLY AMENDED) The method as claimed in claim 52, wherein the reporter gene encodes a color marker and the color marker is a fluorescent marker.

56. (PREVIOUSLY PRESENTED) The method as claimed in claim 55, wherein the fluorescent marker is Green Fluorescent Protein.

57. (CURRENTLY AMENDED) The method as claimed in claim 52, wherein the reporter gene encodes a phage receptor protein or a fragment thereof and the phage is phage λ or *lamB*.

58. (CURRENTLY AMENDED) The method as claimed in claim 22, wherein the ~~bacterial strain is an *E. coli* strain~~ bacteria is *E. coli* or a bacterial cell deficient in endogenous adenylate cyclase.

59. (CURRENTLY AMENDED) The method as claimed in claim 38, wherein the ~~bacterial strain is an *E. coli* strain~~ bacteria is *E. coli* or a bacterial cell deficient in endogenous adenylate cyclase.

60. (CANCELED)

61. (PREVIOUSLY PRESENTED) The method as claimed in claim 34, wherein the signaling molecule is cAMP.

62. (PREVIOUSLY PRESENTED) The method as claimed in claim 35, wherein the signaling molecule is cGMP.

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